GAVIN PUBLISHERS

Journal of Digestive Diseases and Hepatology

He S, et al. J Dig Dis Hepatol 2017: JDDH-123.

Review Article

The Role of Complement in Alcoholic Liver Disease

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Citation: Lin C, Hu Z, Lei B, Tang B, Jin J, He S (2017) TheRole of Complement in Alcoholic Liver Disease. J Dig Dis Hepatol 2016: JDDH-123.

Received Date: 29 December, 2016; **Accepted Date:** 16 January, 2017; **Published Date:** 23 January, 2017

Abstract

The complement system is a key component of the body's immune system. When abnormally activated, the system can induce inflammation and damage to normal body tissues and participate in the development and progression of a variety of diseases. In the past, most scholars believed that alcoholic liver disease(ALD) is due to the stress of ethanol on liver cells, including oxidative stress and dysfunction of mitochondria and protease bodies, causing hepatocyte injury and apoptosis.Recently, studies have shown that complement activation is also involved in the genesis and development of ALD.This article reviews the roles of complement activation in ALD and of therapeutic intervention in complement-activation pathways. We intend to provide new ideas on the diagnosis and treatment of ALD.

Abbreviations

ALD: Alcoholic Liver Disease

FH: Factor H

FI: Factor I

FB: Factor B

MASP: MBL-Associated Proteases

Crry: Complement receptor 1-related protein y

MAC: Membrane Attack Complex

DAF: Decay Accelerating Factor

MCP: Membrane Cofactor Protein

Introduction

Liver disease caused by long-term excessive ethanol drinking is a major cause of chronic liver disease. As the global incidence of alcoholic liver disease (ALD) increases year by year, it has become a serious threat to human health. Almost all heavy drinkers have fatty liver, 10%–20% of which develop into alcoholic hepatitis, cirrhosis, and even hepatocellular carcinoma [1]. Exploration of the mechanisms of alcohol-induced liver injury and repair is extremely important in developing methods for preventing and treating ALD.

The complement system plays an important beneficial role in the immune apparatus: complement activation promotes target-cell lysis, with the associated elimination of exogenous pathogens. Yet, the complement system is a "double-edged sword", as the excessive activation of complement can induce inflammation and lead to autoimmune diseases, such as autoimmune kidney disease, glomerular nephritis, acute lung injury, and others [2-4]. Most plasma complement components are synthesized in liver cells. Thus, the liver becomes the main target of damage by complement activation. Several studies have illustrated that complement activation is involved in the development of ALD [5-11].

Metabolic pathways of ethanol

Most ingested ethanol is absorbed into the blood circulation, and soon reaches every organ of the body. About 90% of the ingested ethanol is metabolizedin the liver [12], and most is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to form acetic acid, which can be used as substrate in the tricarboxylic acid cycle to produce energy. With excessive drinking, the body can activate another metabolic pathway, i.e., the microsomal ethanol oxidation system (MEOS), which catalyzes ethanol mainlyby cytochrome P450 2El (CYP2E1) in Kupffer cells. The MEOS can lead to the overproduction of reactive oxygen species and reactive nitrogen species, which may exceed the body's antioxidant capacity. Free radicals produced via the MEOS pathway promote

a series of toxic effects: membrane-lipid peroxidation, intracellular protease degeneration, oxidative modification of DNA, and others, which eventually lead to necrosis or apoptosis of hepatocytes [11, 13-15].A small percentage of ethanol is metabolized by fatty acid ethyl ester synthase to produce fatty acid ethyl ester through the non-oxidative pathway.Fatty acid ethyl ester has cytotoxicity, which can further injure the liver and pancreas[16]. Thus the liver becomes the main organ damaged by ethanol. Chronic ethanol exposure results in decreased protease activityin liver cells, imbalanceof the liver'sdetoxification function, and overproduction of acetaldehyde, thus inducing hepatic oxidative stress and complement activation; all these activities can injure hepatocytes [17].

Complement activation pathway

The complement system consists of more than 30 kinds of immunoglobulinswith enzyme-like activity whichare inherent components,regulatory proteins, and complement receptors. Complement regulatory proteins include plasma soluble factors (properdin,Factor H, Factor I, and protein S), membrane binding proteins (decay accelerating factor and membrane cofactor proteins), homologous restriction factor, and membrane inhibitors of reactive lysis. Complement receptors expressed on cell membranes bind with complement fragments produced in the process of complement activation, mediating various biological effects. Because the complement systemis involved in inflammation and immune regulation,itplays an important role in regulation of pathophysiological functions. [18]Most complement proteins are synthesized in liver cells; only a small portion is synthesized in endothelial cells, intestinal epithelial cells, and glomerular cells.

Complement is activated by three pathways: the classical, mannan-binding lectin (MBL), and alternative pathways. The three pathways start with differentmechanisms, but they end with a common terminal pathway, asshown in Fig.1. The classical pathway is the main mechanism of immune responses. In it, C1q identifies immune complexes, followed by the activation of C1r and C1s. ActivatedC1scleaves C2 and C4 to form C3 convertase (C4bC2a), which cleaves C3 to form C5 convertase (C4bC2aC3b). In contrastto activation of the classical pathway, activation of the lectin pathway does not depend on immune complexes. In this pathway, the cascade ofenzymatic reactions proceeds in this sequence: MBL identifies the pathogens to form MBL-associated serine proteases (MASP1, MASP2); MASP1 directly cleaves C3 to form C3 convertase (C3bBb), which then is involved in the positive feedback loop of the alternative pathway. MASP2cleaves C4 and C2 in a manner similar to that of C1s, forming C3 convertase(C4bC2a), which continues to cleave C5 to form C5 convertase(C4bC2aC3b). Thus, this pathway can cross-promote the classical and alternative pathways.The alternative pathway is activated with C3, factor B and Factor D, the activation of which is also independent of immune complexes, and participates in the defense mechanisms of the early stage of inflammation [10, 19-21]. The above three pathways merge into the terminal pathway, in which C5 convertase cleaves C5 to form C5a and C5b, and C5b combines with C6, C7, C8 and C9 to form the membrane attack complex (MAC). Formation of the MAC leads to cell lysis and induces cells to release inflammatory cytokines.

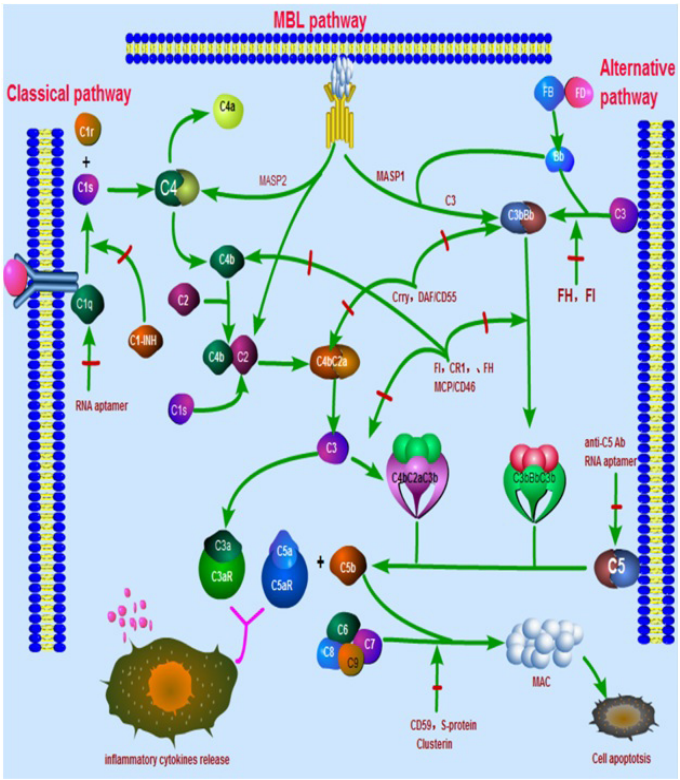

Figure 1: Complement activation pathway and regulation. Three pathways (classical, pathway, MBL, and alternative) are involved in complement activation. Green arrows without a red line indicate the process of complement activation. Green arrows with red line indicate the complement regulatory proteins that inhibit complement activation.

Complement activation in alcoholic liver disease

ALD progresses through three distinct stages: fatty liver, alcoholic hepatitis, and fibrosis/cirrhosis. In this review, we cite evidence that the complement system is involved in the pathogenesis of each of these stages.

Complement activation in alcoholic fatty liver disease

The liver is the main site of fat metabolism. Disorders of fat metabolism, caused by various factors, can lead to excessive fat accumulation in the liver cells, i.e., fatty liver. Long-term

heavy drinking is the main independent risk factor of fatty liver disease[22], but its pathogenesis is not clearly defined. Abnormal activation of complement reportedly enhances the sensitivity of the liver to fat, which leads to the development of fatty liver[23]. Järveläinen, et al.[6] found that deposition of complement C1, C3, and C8 was increased,and the expression of membrane-binding proteins complement receptor 1-related protein y(Crry) and CD59 was decreased in the liver cells of a mouse ALD model. These findings are evidence that alcohol-induced complement activation can result in ALD, at least in an experimental model.In other studies in mice chronically exposed to ethanol,Cohen, et al. [10] found that lipid deposition in liver cells as well as values of liver-related serum enzymes (alanine aminotransferase and aspartate amino transferase) increased significantly; various degrees of liver cell apoptosis were also found. Moreover, with knock out of the C1q gene, hepatic steatosisin the mice was significantly decreased[10]. This study illustrated that complement activation could be associated with ethanol-induced hepatic steatosis.

Bykov, et al. [7] fed C3+/+ and C3-/- mice a high fat and high alcohol diet, respectively. The authors found that hepatic steatosis and significant increases in triglyceride values developed in the C3+/+mice,whereas C3-/-mice were protected from ethanol-induced liver injury;research by Stewart,et al. [5] yielded similar results. Thus, activation of complement C1 and C3 appears to play a significant role in promoting fatty infiltration in the liver. Further definition of the relationship between activated complement C1, C3 and lipid metabolism in the liver may aid in the development of measures for intervention and treatment of alcoholic fatty liver disease.Besides C1 and C3,complement C5 also is involved in lipid metabolism.Bavia, et al.[24, 25] found the activation of complement C5 by high-dose ethanol exposure can affect the distribution of lipid in liver cells and serum: Less lipid and cholesterol is deposited in hepatocytes of C5- mice than in hepatocytes of C5+mice, and values of IL-17, which is involved in the synthesis and metabolism of lipid and cholesterol,are higher in C5- mice than in C5+mice [26, 27].The above-cited reports indicate that activation of C5 likely plays a role in the development of alcoholic fatty liver.

Complement activation in alcoholic hepatitis

ALD has many potential pathogenic factors, such as endotoxin, which may lead to complement activation and deposition in the liver cells. Also, oxidative stress aggravates the tissue injury in alcoholic hepatitis [28-30].Cohen, et al. [10] found that long-term alcohol exposure can lead to apoptosis of liver cells, and the degree of apoptosis is positively correlated with liver injury. However,whether short-term alcohol exposure can cause hepatocyte apoptosis was not known. Further research resolved this issue: Short-term alcohol exposure did not cause hepatocyte apoptosis, but it did promote the deposition of complement C3b and the expression of inflammatory cytokines (tumor necrosis factor and IL6). After theCq gene was knocked out, the expression of inflammatory cytokines was significantly reduced compared to that in wild-type animals [9, 10]. Experiments by Païdassi, et al. [31] and Lu, et al. [32] supported these observations.

Complement C5, a core component of the complement activation pathway,is involved in the occurrence and development of alcoholic hepatitis, in addition to fatty liver[8, 33,34].Bavia, et al.[33]documented thisina hepatitis model induced by alcohol; they found that values of pro-inflammatory cytokines (IL-6, IFN-γ, IL-1β, and others) in B6C5+ mice were significantly higher than those in B6C5- mice, and anti-inflammatory factors (IL10 and IL17) were secreted significantly more in B6C5- mice. These findings illustrated that activated C5 induced the expression of proinflammatory cytokines after alcohol exposure. Up-regulated expression of pro-inflammatory cytokines (IL-6, IFN-γ, IL-1β, and others) aids the body'sdefense against pathogenic microorganisms, but it also participates in the pathogenesis of alcoholic fatty liver and alcoholic hepatitis [8, 35-37].

Complement activation in alcoholic hepatic fibrosis

Intrahepatic inflammatory reaction and a decrease in structural integrity of hepatic sinusoidal endothelial cells after long-term alcohol exposure are important inducements to liver injury. Sinusoidal endothelial cells express C5R1, which is the foundation of C5 activation-induced alcoholic hepatic fibrosis [38]. In recent years, the pathogenesis of alcoholic hepatic fibrosis has attracted wide attention internationally, but the cause of the fibrosis is still not fully defined [39-41].According to published reports, [42, 43] complement C3, C4 and activation of the MBL pathway are involved in the development of fibrosis. Bavia, et al.,[33] using the mouse model of ALD, found that values of TGF-β,which promotes hepatic fibrosis, were significantly higher in B6C5+ mice than in B6C5- mice [33, 44]. Hillebradt, et al.[45] found the C5 gene involved in the regulation of hepatic fibrosis on human chromosome, and further study found that C5- mice have decreased hepatic fibrosis. Thus, the evidence indicates that activation of complement C5 likely promotes hepatic fibrosis. Exploration of the relationship between complement activation and alcoholic hepatic fibrosis, and of possible intervention in ALD by reversing the progression of hepatic fibrosis in its early stage, seems worthwhile goals.

Complement-induced Kupffer cells and alcoholic liver disease

Kupffer cells, located in liver sinusoids, are an important part of the mononuclear phagocyte system. Alcohol exposure in

the early stage can promote apoptosis of Kupffer cells,but longer exposure usually is needed [10, 46,47].Ethanol-induced activation of complement component C1q at the early stage of ALD promotes the release of inflammatory cytokines from Kupffer cells, which further promote alcoholic liver injury[47-52]. Furthermore,Kupffer cells can express C3R and C5R,then induce prostaglandin release and synthesis of pro-inflammatory cytokines [53-56].However,in certain pathological conditions,activated C5 combines with C5R, inducing the upregulation of fibrinogenon Kupffer cells, an interaction that is believed to lead to hepatic fibrosis [19, 57]. In addition,alcohol-induced upregulation of CD14 leads to Kupffer cells combining with lipopolysaccharide, which induces liver damage through the activation of TLR4 in Kupffer cells and inflammatory signaling pathways; these events can further aid in the development of hepatic fibrosis or cirrhosis [58]. Thus, Kupffer cells seem to be extensively involved in the development of ALD [59-62].

Complement regulation in alcoholic liver disease

Reducing inflammatory reactions by inhibiting amplification of the complement cascade and blockingthe combination of complement withthe corresponding complement receptors is being pursued worldwide. Excessive activation of complement can be inhibited by self-regulation of the body (Table 1). For example, the complement regulatory protein decay accelerating factor (DAF) can inhibit C3,C5 convertase,thereby inhibiting amplification of the complement cascade. The complement regulatory protein Crry can cooperate with DAF and Factor H, to accelerate dissociation of C3, C5 convertase and to cleave C3b, C4b, so that the body's cells avoid being attacked by autologous complement [63-65]. Deficiency of CD55/DAF and complement regulatory factors aggravate liver injury [7, 8], whereas FactorH can control the activity and stability of C3convertase via binding with C3b [66, 67]. Also, defects in the Factor H gene can cause persistent activation of complement pathways and trigger various diseases [68-71]. By contrast, Factor H-related proteins (FHRs), including FHR1–5, can either promote or inhibit complement activation. The degree of complement activation depends on the homeostasis between-Factor H and FHR [67]. However, the relationship between Factor H and ALD has not been clarified and needs further research. In other complement regulatory activities, CD59, protein S and clusterininhibit the formation of the MAC through limiting the binding of complement C9 [72-76].Membrane cofactor protein (MCP) and Factor I can inhibit cells from binding with C3b and C4b [77, 78].

Type of regulator	Regulator	Function
Complement regulatory protein	DAF/CD55, Crry, FH, FI	Inhibit C3, C5 convertase
Complement inhibitor	CD59, protein S, clusterin C1-INH	Inhibit MAC
Targeted inhibitor	h5G1, 1-ScFv	Inhibit C1r, C1s
RNAaptamer	Specifically bind C1q, C5	Inhibit C5 activation

Table 1: Complementregulators.

Specific epitope structures of complement, such as anti-complement antibody, complement antisense strand, and complement mutants [79-86]have been invented, with the intent of inhibiting complement activation. In addition, complement inhibitors and RNA aptamer are being used to inhibit progression of complement-related diseases[87, 88], andC1-INH and CR1 have been used in the treatment of ALD and other diseases[6].

Summary

Mounting evidence indicates that complement activation is involved in the development of ALD at all its stages-fatty liver, alcoholic hepatitis, and fibrosis/cirrhosis. Moreover, all three pathways of complement activation (classical, mannan-binding lectin, and alternative) promote the development of ALD.Therapeutic strategies, using various measures to inhibit complement activation, might prevent the development of ALD, but these strategies cannot be limited a single complement component. Thorough understanding of the relationships between complement activation and ALD may aid in developing new approaches for the treatment of ALD.

Disclosure of Potential Conflicts of Interest

The authors disclose no potential conflicts of interest.

Acknowledgments

This work was supported in part by The National Natural Science Foundation of China (No. 81430014 and No. 31370917), the Natural Science Foundation of Guangxi Province (2015GXNSFFA139004 and 2014GXNSFDA118019,The Bagui Scholarship Foundation.Guangxi health and Family planning commission "139"leading talents training plan.

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